December 11, 2001

Timothy Adams
The Flavor and Fragrance High Production Volume Consortia
1620 I Street N.W.
Suite 925
Washington, DC 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxic Substances is transmitting EPA's comments on the robust summaries and test plan for "C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids", posted on the ChemRTK Web Site on, June 21, 2001. I commend The Flavor and Fragrance High Production Volume Consortia for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA agrees with the category approach and test plan. However, the submitter should provide additional information on metabolism of a branched aldehyde, 2,6-dimethyl-5-heptenal (whether it is similar to the straight-chain aldehydes) to justify its use as an analog to support the category.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that The Flavor and Fragrance High Production Volume Consortia advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson

C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids

SUMMARY OF EPA COMMENTS

The sponsor, the C_6-C_{10} Consortium of the Flavorings and Fragrances High Production Volume Consortia, submitted a test plan and robust summaries to EPA for C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids. EPA posted the submission on the ChemRTK website on 21 June 2001.

EPA has reviewed this submission and reached the following conclusions:

1. Category Justification. The justification for grouping three straight-chain aldehydes and a carboxylic acid (heptanoic acid) appears appropriate. However, using analog data on 2,6-dimethyl-5-heptenal to support the category is not adequately justified for health effects endpoints. Additional information is needed on how a branched aldehyde is a suitable analog; for example, whether its metabolism is similar to that of other members of the category.

2. Physicochemical and Environmental Fate Data. EPA agrees with the category approach and test plan for these endpoints.

3. Health Endpoints. The health effects data were adequate for acute toxicity, genetic toxicity, and developmental toxicity endpoints. The data for reproductive toxicity endpoints are adequate for the shorter-chain members of the category and these results can reasonably be extrapolated to the longer-chained members of the category. For the repeated-dose toxicity endpoint, data on an analog are used; additional information is needed to justify its use.

4. Ecological Effects. The measured environmental effects data for heptanal appear adequate and agree with ECOSAR predictions. EPA agrees with the proposed testing of nonanal in daphnia and algae.

EPA requests that the Submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON C_6-C_{10} ALIPHATIC ALDEHYDES AND CARBOXYLIC ACIDS CATEGORY CHALLENGE SUBMISSION

Category Definition

The Submitter has defined the C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids category as ". . . a homologous series of straight chained saturated aldehydes of carbon chain lengths C_7 to C_9, heptanal, octanal, nonanal and one structurally related carboxylic acid, heptanoic acid."

It is unclear why the category is named "C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids" when the chemicals discussed in the test plan contain carbon chain lengths of C_7 to C_9. Although data for hexanal and decanal support the category and the sponsor is the C_6-C_{10} Consortium, the category name should reflect the range of chemicals in it.

Category Justification

The rationale for grouping C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids is based on their close structural similarities, physicochemical properties, and their metabolic fate. As this group represents a homologous series and the structural similarities of the aldehydes are clear, it is anticipated that the aldehydes in this category will show regular physicochemical property trends.

The Submitter describes the *in vivo* metabolic pathways for the linear, short-chain aldehydes and their corresponding carboxylic acids. This description appears to support the contention that (1) aldehydes are easily oxidized to their respective carboxylic acid derivatives in a number of environmental settings; (2) enzymatic pathways common to a number of organisms efficiently oxidize aldehydes to the corresponding carboxylic acids *in vivo*; and (3) once converted, these carboxylic acids can be metabolized to carbon dioxide through catabolism and participation in the tricarboxylic acid cycle or assimilated into other biomolecules through the fatty acid pathway.

The Submitter has used data for 2,6-dimethyl-5-heptenal to support the category. No information is presented in the test plan on the metabolism of the 2,6-dimethyl-5-heptenal. If the metabolic pathway for this chemical is similar to that of the straight-chain aldehydes, then its use as an analog is acceptable.

For ecological effects, the category approach appears to be appropriately based on structure-activity relationships and consistency between the measured and predicted data.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The submitted physicochemical data appear adequate.

Environmental Fate (photodegradation, stability in water, biodegradation, and transport/distribution).

Octanol/Water Partition Coefficient. EPA agrees with the submitter's approach.

Water Solubility. On page 8 of the Test Plan, the submitter reported a literature value of 242 mg/L at 15 °C [Merck, 1997] for heptanoic acid. However, the Merck Index (1996, Twelfth edition, page 797) reports a value of 0.2419 g/100ml at 15 °C, which is equal to 2419 mg/L. The submitter should correct this discrepancy.

Chemical Transport and Distribution in the Environment. The submitter's approach to the environmental fate endpoints is generally acceptable. The submitter has used EQC Fugacity Level I model. However, EPA recommends using the EQC Fugacity Level III model from the Canadian Environment Modeling Centre at Trent University, found at the following Web address: http://www.trentu.ca/academic/aminss/envmodel. A Fugacity Level III model is more realistic and useful for estimating a chemical's fate in the environment.

Biodegradation. The submitted data are adequate for the purposes of the HPV Challenge Program. EPA also agrees with the submitter's plan to test heptanoic acid for its biodegradation potential.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The submitter presented a number of studies that adequately address the potential toxicity of heptanoic acid. In several instances for the aldehydes in the category (heptanal, octanal, and nonanal), hexanal, 2,6-dimethyl-5-heptenal, and a mixture of C_8-C_{12} aldehydes were used as analogs. Hexanal is an acceptable analog based on its structural similarity to the category members. The use of 2,6-dimethyl-5-heptenal as an analog is acceptable (see category justification), if its metabolic pathway is similar to those of the straight-chain aldehydes/carboxylic acids ($-oxidation). This is not discussed in the test plan. Finally, a mixture of C_8-C_{12} aldehydes (incompletely characterized–it is unclear if branched aldehydes are present) is used in one repeated dose toxicity study; this study is considered inadequate. However, adequate repeated-dose toxicity studies on hexanal and 2,6-dimethyl-5-heptenal satisfy this

endpoint, pending additional information. EPA recommends that to the extent that their inclusion can be justified, the final category analysis should include data for hexanal and 2,6-dimethyl-5-heptenal as entries in the category data matrix.

Repeated Dose Toxicity. Of the oral studies representing the aldehyde toxicities, one that used hexanal, and two that used 2,6-dimethyl-5-heptenal appear adequate. However, as stated in the above paragraph, the sponsor should provide additional information on the metabolism of 2,6-dimethyl-5-heptenal to justify its use as an analog for heptanal. The 90-day feeding study that used C_8-C_{12} aldehydes mixture as an analog for octanal and nonanal is inadequate because the study was conducted using a single concentration that was a NOAEL.

Reproductive/Developmental Toxicity. For the reproductive/developmental toxicity endpoint, the adequate studies on heptanoic acid and nonanoic acid are supported by a number of less reliable studies and support the conclusions of the submitter. EPA agrees with the submitter that based on the rapid metabolism of an aldehyde to an acid, the existing studies on acids appear to be appropriate for characterizing the developmental effects of the aldehydes in this category.

Ecological Effects (fish, daphnid, and algal toxicity)

The predicted ECOSAR values for acute toxicity to fish, daphnia, and algae were provided to support the measured data for each of these endpoints. Using SAR to support measured data in this manner is appropriate and consistent with the HPV Challenge guidance for applying structure-activity relationships (http://www.epa.gov/chemrtk/sarfinl1.htm).

SPECIFIC COMMENTS ON THE ROBUST SUMMARIES

General

In the robust summaries, the wording of the substance name/analog is unclear and listing of CAS numbers is also inconsistent. In some cases, the CAS number is that of the analog, but in other cases it is that of the category member. It would be preferable to list the CAS number of the analog and use the analog name as the Substance Name (with the category member in parentheses). For example:

Substance Name	Octanoic acid (analog for heptanoic acid)
CAS No.	124-07-2

Health Effects

In many cases, the robust summaries did not provide complete details for the methods and results, thus limiting the ability to allow an independent assessment of the quality of each study. The summaries for acute studies were commonly missing information on dose levels and test substance purity, and in one acute oral summary, no units were given for the LD_{50} value. The robust summaries for genetic toxicity studies sometimes lacked descriptions of positive controls, test concentrations, statistical methods, and test systems. Although the repeated dose study summaries provided more information, statistical methods and test substance purity descriptions were often missing. The summaries for reproductive and developmental studies provided sufficient information with the exception of test substance purity details.

Environmental Effects

In general, the robust summaries were well prepared and presented the information necessary to understand the study design and results. However, some data elements such as water temperature, total organic carbon content, and dissolved oxygen demand were missing from the summaries. EPA has provided specific comments on how to enhance the robust summaries to the standard established in EPA's HPV Challenge Program Guidance at http://www.epa.gov/chemrtk/guidocs.htm.

Followup Activity

EPA requests that the Submitter advise the Agency within 60 days of any modifications to its submission.